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(71) Applicant *(for all designated States except US)*: ASTRA AKTIEBOLAG [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: SJÖQUIST, Gabrielle [SE/SE]; Astra Draco AB, P.O. Box 34, S-221 00 Lund (SE).

(74) Agent: ASTRA AKTIEBOLAG; Intellectual Property, Patents, S-151 85 Södertälje (SE).

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(54) Title: PHARMACEUTICAL COMPOSITIONS COMPRISING MICELLES COMPRISING LIPOPHILIC GLUCOCORTICOSTEROID AND ONLY ONE SURFACTANT

(57) Abstract

The present invention relates to a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant. The invention further relates to a process for the preparation of the pharmaceutical composition and use of the pharmaceutical composition for the manufacture of a medicament for treating allergic and/or inflammatory diseases in the respiratory tract or for treating intestinal diseases and methods for treatment of the diseases in a mammal, including man.

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PHARMACEUTICAL COMPOSITIONS COMPRISING MICELLES COMPRISING LIPOPHILIC GLUCOCORTICOSTEROID AND ONLY ONE SURFACTANT

FIELD OF INVENTION

The present invention relates to a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant. The invention further relates to a process for the preparation of the pharmaceutical composition and use of the pharmaceutical composition for the manufacture of a medicament for treating allergic and/or inflammatory diseases in the respiratory tract or for treating intestinal diseases and methods for treatment of the diseases in a mammal, including man.

BACKGROUND OF THE INVENTION

Rhinitis and asthma are today effectively treated by the use of glucocorticosteroids such as e.g. mometasone furoate, budesonide, and fluticasone propionate. Patent applications that can be mentioned in this context are WO 92/13873 and WO 96/19199 both to Astra AB of Sweden.

Well-known methods of administering the glucocorticosteroids are by oral and nasal inhalation. The glucocorticosteroid compositions are used in the form of powders in dry powder inhalers, as solutions or suspensions in pressurized metered dose inhalers (pMDIs). A suspension in water is a user-friendly form of administration as the solution is easily accepted by the mucosa. However, in a water suspension the glucocorticosteroid crystals are in contact with the water which can affect the stability of the glucocorticosteroid. A glucocorticosteroid ester may be chemically degraded for example by ester hydrolysis when using such a compound. Further, the compositions in the form of suspensions may be less stable than solutions e.g. due to sedimentation or precipitation. It is also easier to administer a solution accurately in comparison with a suspension.

US 4,994,439 to California Biotechnology discloses aqueous compositions for trans-mucosal membrane administration of protein or peptide drugs wherein the compositions comprise the drug in mixtures with at least one bile salt or fusidate or a derivative thereof and at least one non-ionic detergent of the formula $RO(CHR'CH_2O)_nR$, wherein one R is H and the other R represents the radical of a saturated or unsaturated cyclic or acyclic organic alcohol of 6-40 carbons. The use of a mixture of carrier components results in the formation of mixed micelles, exhibiting transport efficiencies across mucous membranes comparable to or better than those achieved using bile salts/fusidates alone. Detergents on their own are said to be poor absorption promoters.

EP 0179583 A1 to Merck & Co. Inc. discloses a system for enhancing the water dissolution rate and solubility of poorly soluble drugs. The compositions of EP 0179583 A1 involve combining the poorly water-soluble drug with the surfactant in appropriate ratios and by an appropriate method that results in the formation of an anhydrous product. The examples are directed to anhydrous compositions of the antiparasitic agents ivermectin or abamectin and a surfactant.

It is an object of the present invention to provide a stable aqueous solution of a lipophilic glucocorticosteroid for use as a medicament, especially for treating allergic and/or inflammatory diseases in the respiratory tract and also for treating intestinal diseases such as inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease.

It is a further object of the invention to provide a process for the preparation of such a stable solution.

SUMMARY OF THE INVENTION

According to the invention there is provided a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

According to a preferred embodiment the composition comprises one and only one non-ionic surfactant.

According to another preferred embodiment the composition is used for treating allergic and/or inflammatory diseases in the respiratory tract.

According to yet another preferred embodiment the composition is used for treating intestinal diseases.

According to a further aspect of the invention a process for the preparation of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant, the process comprising the steps of:

a) dissolving the glucocorticosteroid in the surfactant;

b) adding an aqueous medium to the solution from step a) and stirring the solution.

According to yet another aspect of the invention use of a composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant, for the manufacture of a medicament for treating allergic and inflammatory diseases in the respiratory tract is obtained.

According to a further aspect of the invention use of a composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and

one and only one pharmaceutically acceptable surfactant for the manufacture of a medicament for treating intestinal diseases is obtained.

Another aspect of the invention is a method for treatment of allergic and/or inflammatory diseases in the respiratory tract of a mammal, including man. The method is characterized by administration to the mammal in need of such treatment of an therapeutically effective amount of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

A last aspect of the invention is a method for treatment of intestinal diseases in a mammal, including man. The method is characterized by administration to the mammal in need of such treatment of an therapeutically effective amount of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention it was found that lipophilic glucocorticosteroids and their esters can be incorporated in micelles formed by a surfactant, especially a non-ionic surfactant, in an aqueous medium. According to "Pharmaceutical Dosage Forms; Disperse Systems", vol.1, p.315 ff (1988) ed. by H.A. Lieberman et al, micelles are molecular aggregates formed in the solution of a surfactant. Surfactants in a dilute aqueous solution exist primarily as monomers, but at higher concentrations a number of surfactant molecules aggregate to form micelles. Thereby a stable formulation is obtained in which the lipophilic glucocorticosteroid/glucocorticosteroid ester is protected and is possible to be absorbed.

The micelles will act as non-aqueous reservoirs for the lipophilic glucocorticosteroid and will positively affect the pharmacokinetic and deposition of the glucocorticosteroid molecule. The glucocorticosteroid will also be more easy to dose accurately as well as for

the patient to administer accurately. For further information of the expression "lipophilic" reference can be made to the above mentioned reference where on p. 155 it is stated that "lipophilic drugs may be wetted by oils and semipolar liquids."

The problem with preparation of compositions comprising the lipophilic glucocorticosteroids used in the invention in an aqueous medium is that they are very difficult to dissolve in water and then to obtain a stable composition. It was found in the present invention that by dissolving the lipophilic glucocorticosteroid in a surfactant, preferably a non-ionic surfactant, stable compositions can be obtained with the glucocorticosteroid in micellar form.

The inventor of the present invention, has further found that use of the stable compositions comprising e.g. rofleponide palmitate incorporated in micelles formed by a surfactant, causes less irritation in the lung after oral inhalation by human patients, than is experienced after oral inhalation of the same surfactant on its own.

The present compositions comprise one and only one surfactant. The surfactant used in the present compositions can be non-ionic, zwitterionic, anionic or cationic. It is, however, preferred, to use a non-ionic surfactant, since this normally reduces the risk of side-effects after administration. Examples of non-ionic, zwitterionic, anionic or cationic surfactants which may be used in the present invention can be found in Wade and Weller, Handbook of Pharmaceutical Excipients, 1994, The Pharmaceutical Press, London.

The non-ionic surfactants used according to the present invention are suitably selected from poloxamers, e.g. poloxamer 188; polyoxyethylene alkyl ethers, e.g. poloxyl 10 stearyl ether, poloxyl 20 stearyl ether; polyoxyethylene stearates, e.g. polyoxyl 8 stearate, poloxyl 12 stearate; polyoxyethyleneglycol hydroxystearates, e.g. polyoxyethyleneglycol 12-hydroxystearates, and polyoxyethylene sorbitan fatty acid esters. A preferred group of non-ionic surfactants is polyoxyethylene sorbitan fatty acid esters, e.g. polyoxyethylene 20 sorbitan monolaurate, monopalmitate, monostearate or monooleate also known as poly-

sorbate 20, polysorbate 40, polysorbate 60 and polysorbate 80, respectively Examples of suitable commercial polysorbates are Tween™ 20, Tween™ 40, Tween™ 60 and Tween™ 80.

A further preferred group of non-ionic surfactants is polyoxyethyleneglycol 12-hydroxy-stearates and an especially preferred compound is polyoxyethyleneglycol 660 12-hydroxy-stearate.

In the present invention, lipophilic glucocorticosteroids relate to lipophilic glucocorticosteroids *per se*, as well as their pharmaceutically acceptable solvates, esters, acetals and salts, and solvates of any of these.

Examples of glucocorticosteroids which may be used in the present invention include betamethasone, fluticasone (e.g. as propionate), budesonide, tipredane, dexamethasone, beclomethasone (e.g. as dipropionate), prednisolone, fluocinolone (e.g. as acetonide), triamcinolone (e.g. as acetonide), mometasone (e.g. as furoate), rofleponide (e.g. as palmitate), flumethasone, flunisolide, ciclesonide, deflazacort, cortivazol, 16α,17α-butylidenedioxy-6α,9α-difluoro-11β,21-dihydroxy-pregna-1,4-diene-3,20-dione; 6α,9α-difluoro-11β-hydroxy-16α,17α-butylidenedioxy-17β-methylthio-androsta-4-ene-3-one; 16α,17α-butylidenedioxy-6α,9α-difluoro-11β-hydroxy-3-oxo-androsta-1,4-diene-17β-carbothioic acid S-methyl ester; methyl 9α-chloro-6α-fluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17α-carboxylate; 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy-androsta-1,4-diene-17β-carbothioic acid S-(2-oxo-tetrahydrofuran-3-yl) ester; optionally in their pure isomeric forms (where such forms exist) and/or in the form of their pharmaceutically acceptable solvates, esters, acetals or salts, or where applicable solvates of any of these. Suitably, use is made of mometasone furoate, beclomethasone dipropionate or fluticasone propionate or glucocorticosteroids with an asymmetric acetal structure, e.g. comprising 16α,17α-butylidenedioxy group, such as budesonide or rofleponide or pharmaceutically acceptable solvates, esters, acetals or salts, or where applicable, solvates thereof. The most preferred lipophilic glucocorticosteroid ester is rofleponide palmitate.

The amount of surfactant used in the composition should be less than 5 % (w/w) of the total composition weight. Preferably the amount of surfactant is less than 3 % (w/w) and most preferably less than 1 % (w/w) of the total composition weight. The concentration of the surfactant must, however, be higher than the critical micellar concentration (CMC), being the lowest concentration at which micelles are formed in an aqueous medium. The CMC value depends primarily upon the temperature and the concentration of possible additives. It lies within the competence of the skilled person to determine the CMC for each indivi-dual composition and thus prepare suitable micelles according to the present invention.

The amount of the glucocorticosteroid used depends on the field of use. If the glucocorticosteroid is used for treating diseases in the respiratory tract by inhalation a suitable daily dose is from 10 to 2400 µg, preferably from 10 to 1600 µg. If the glucocorticosteroid is used for treating intestinal diseases a suitable daily dose is from 400 to 4000 µg, preferably from 800 to 3000 µg.

The composition according to the invention may also contain one or more pharmaceutically acceptable additives such as buffers and other pH modifiers, antioxidants, complexing agents to further increase the stability, viscosity regulating agents and isotonicity modifying agents. Compounds used as such agents are compounds generally used in drug formulations e.g. EDTA for complexing and carboxymethyl cellulose (CMC) for regulating viscosity. As substances for adjusting the isotonicity can be mentioned glucose, mannitol, salts, glycerol and propylene-glycol. Preferably alkaline buffers are used such that the pH of the composition is from 4 to 7. It is, however, preferred to use one or more antioxidant(s), which may be water-soluble to a smaller or larger degree. Examples of such antioxidants include, without limitation, tocopherols, especially α-tocopherol, and preferably racemic α-tocopherol, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT) and ascorbic acid.

In order to prepare the aqueous composition according to the present invention the glucocorticosteroid drug has to be dissolved in a first step. It was found in the present invention that a stable composition of the glucocorticosteroid is obtained if the glucocorticosteroid is dissolved in the surfactant. Then the aqueous medium is added to the glucocorticosteroid-surfactant solution and the mixture is stirred, preferably intensely stirred, to obtain a stable and homogeneous solution. Preferably the aqueous medium is of the same temperature as the one of the glucocorticosteroid-surfactant solution before it is added to the solution. If other pharmaceutically acceptable additives are used they are suitably added to the aqueous medium before mixing with the glucocorticosteroid-surfactant solution if they are water soluble. Otherwise they are added to the surfactant solution. In a preferred embodiment of the process glucose is dissolved in the aqueous medium in an isotonic amount.

The surfactant used can be a solid compound at ambient temperature or a more or less fluid compound. If a solid surfactant is used it should be heated in order to melt it in a first step of the process. The glucocorticosteroid is then dissolved in the melted surfactant. This is a preferred embodiment of the invention.

If the surfactant is fluid enough the glucocorticosteroid can be dissolved directly in the surfactant at ambient temperature or it may be suitable to increase the temperature of the surfactant to more readily dissolve the glucocorticosteroid. Then the water is added.

A further possibility is to dissolve the surfactant in a conventional organic solvent, e.g. ethanol, and then to dissolve the glucocorticosteroid in this solution or vice versa. The organic solvent then has to be evaporated before the aqueous medium is added. It is important that the organic solvent is removed from the composition otherwise the composition will have a stinging effect in the nose of the patient if the composition is used for the manufacture of a medicament for treating allergic and/or inflammatory diseases in the respiratory tract.

Optionally the composition according to the invention can be made sterile in a conventional manner, e.g. by using dry heat, steam or irradiation.

The composition according to the invention is used for the manufacture of a medicament for treating allergic and/or inflammatory diseases in the respiratory tract. The composition can then be administered via the upper and lower respiratory tract, including nasal or oral inhalation. The composition according to the invention can be used in common devices for aqueous solutions for nasal and oral inhalation e.g. in a spray pump or in a nebulizer. For administration by nebulisation reference is made to "Medication Nebulizer Performance", Chest 110(2), (1996), pp. 498-505. The composition according to the invention is also used for the manufacture of a medicament for treating intestinal diseases such as inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease. The compositions can then be administered by rectal administration.

The invention also relates to a method for treatment of allergic and/or inflammatory diseases in the respiratory tract of a mammal, including man. The composition according to the invention is administered in a therapeutically effective amount to the mammal in need of such a treatment, preferably by nasal or oral inhalation.

The invention also relates to a method of treatment of intestinal diseases in a mammal, including man. The composition according to the invention is administered in a therapeutically effective amount to the mammal in need of such a treatment, preferably by rectal administration.

The invention will now be illustrated by the following non-limiting example:

EXAMPLE

Manufacturing of rofleponide palmitate in micellar solution.

5 g Solutol® HS15 (polyethyleneglycol 660 12-hydroxystearate) manufactured by BASF of Germany is melted in a beaker at 35°C-40°C. 100 mg rofleponide palmitate is added to the melt and dissolved.

An isotonic solution of 25 g glucose in 495 g water is heated to 35-40°C and added to the melt using intense stirring. A clear solution containing 0.2 mg rofleponide palmitate/ml is obtained.

CLAIMS

1. A pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

2. The composition according to claim 1 or 2, wherein the surfactant is a non-ionic surfactant.

3. The composition according to claim 2, wherein said non-ionic surfactant is selected from the group consisting of poloxamers, polyoxyethylene alkyl ethers, polyoxyethylene stearates, polyoxyethyleneglycol hydroxystearates and polyoxyethylene sorbitan fatty acid esters.

4. The composition according to claim 3, wherein the non-ionic surfactant is a polyoxyethyleneglycol 12-hydroxystearate.

5. The composition according to claim 4, wherein the non-ionic surfactant is polyoxyethyleneglycol 660 12-hydroxystearate.

6. The composition according to claim 3, wherein the non-ionic surfactant is polysorbate 20, polysorbate 40, polysorbate 60 or polysorbate 80.

7. The composition according to any previous claim, wherein the glucocorticosteroid is selected from the group consisting of mometasone furoate, beclomethasone dipropionate, fluticasone propionate, glucocorticosteroids with an asymmetric acetal structure involving a 16α,17α-butylidenedioxy group, and pharmaceutically acceptable solvates, esters, acetals and salts, and solvates of any of these.

8. The composition according to claim 7, wherein the glucocorticosteroid is roflepo-nide palmitate.

9. A composition according to any previous claim, wherein the amount of the surfac-
5 tant is less than 5 % (w/w) of the total composition weight, preferably less than 3 % (w/w), more preferably less than 1 % (w/w) of the total composition weight.

10. A composition according to any previous claim, wherein the composition further comprises one or more pharmaceutically acceptable additives selected from the group
10 consisting of antioxidants, isotonicity modifying agents, pH modifiers, complexing agents and viscosity regulating agents.

11. A composition according to claim 10, wherein the isotonicity modifying agent is glucose.

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12. A composition according to claim 10, wherein the antioxidant is selected from the group consisting of tocopherols, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT) and ascorbic acid.

20 13. A process for the preparation of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant, the process comprising the steps of:

a) dissolving the glucocorticosteroid in the surfactant; and

25 b) adding the aqueous medium to the solution from step a) and stirring the solution.

14. The process according to claim 13, wherein the surfactant is a non-ionic surfactant.

15. The process according to claims 14, wherein said non-ionic surfactant is selected
30 from the group consisting of poloxamers, polyoxyethylene alkyl ethers, polyoxyethylene-

stearates, polyoxyethyleneglycol hydroxystearates and polyoxyethylene sorbitan fatty acid esters.

16. The process according to claim 15, wherein the non-ionic surfactant is a polyoxyethyleneglycol 12-hydroxystearate.

17. The process according to claim 16, wherein the non-ionic surfactant is polyoxyethyleneglycol 660 12-hydroxystearate.

18. The process according to claim 15, wherein the polyoxyethylene sorbitan fatty acid ester is selected from the group consisting of polysorbate 20, polysorbate 40, polysorbate 60 or polysorbate 80.

19. The process according to any one of claims 13-18, wherein the glucocorticosteroid is selected from the group consisting of mometasone furoate, beclomethasone dipropionate, fluticasone propionate, glucocorticosteroids with an asymmetric acetal structure involving a 16α,17α-butylidenedioxy group, and pharmaceutically acceptable solvates, esters, acetals and salts, and solvates of any of these.

20. The process according to claim 19, wherein the glucocorticosteroid is rofleponide palmitate.

21. The process according to any one of claims 13-20, wherein the amount of the surfactant is less than 5 % (w/w) of the total composition weight, preferably less than 3 % (w/w), more preferably less than 1 % (w/w) of the total composition weight.

22. The process according to any of the claims 13-21, wherein the composition further comprises one or more pharmaceutically acceptable additives selected from the group consisting of antioxidants, isotonicity modifying agents, pH modifiers, complexing agents and viscosity regulating agents.

23. The process according to claim 22, comprising dissolving glucose in an isotonic amount in the aqueous medium before adding the aqueous medium to the solution from step a).

24. Use of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant, for the manufacture of a medicament for treating allergic and/or inflammatory diseases in the respiratory tract.

25. Use according to claim 24, wherein the daily dose of the glucocorticosteroid lies in the range of from 10 to 2400 µg, preferably from 10 to 1600 µg.

26. Use of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant, for the manufacture of a medicament for treating intestinal diseases.

27. Use according to claim 26, wherein the daily dose of the glucocorticosteroid lies in the range of from 400 to 4000 µg, preferably from 800 to 3000 µg.

28. Use according to any one of claims 24 to 27, wherein the composition is as defined in anyone of claims 2-12.

29. A method for treatment of allergic and/or inflammatory diseases in the respiratory tract of a mammal comprising administering to the mammal in need of such a treatment a therapeutically effective amount of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

30. A method for treatment of intestinal diseases in a mammal, comprising administering to the mammal in need of such a treatment a therapeutically effective amount of a pharmaceutical composition comprising micelles in an aqueous medium, wherein the micelles comprise a lipophilic glucocorticosteroid and one and only one pharmaceutically acceptable surfactant.

31. A method for treatment according to claim 29 or 30, wherein the composition is as defined in anyone of claims 2-12.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02426

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 9/107, A61 9/127, A61K 9/133, A61K 31/56, A61K 31/565, A61K 31/57, A61K 31/575, A61K 31/58
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, EPODOC, TXTE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4994439 A (JOHN P. LONGENECKER ET AL), 19 February 1991 (19.02.91), see especially column 7, rows 6-16, column 4, rows 28-29, column 2, rows 50-60, claim 15, column 8, rows 5-61, column 8, rows 31-34	1-3,7-17, 24-31
Y		4-6,13-23
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Y	EP 0179583 A1 (MERCK & CO. INC.), 30 April 1986 (30.04.86), see especially page 5, rows 28-34 and page 9, rows 31 - page 10, row 13	4-6,13-23
	--	
A	WO 9619199 A1 (ASTRA AKTIEBOLAG), 27 June 1996 (27.06.96), see especially claim 15	8,20
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 April 1999	26 -04- 1999
Name and mailing address of the ISA/ Swedish Pat nt Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Anneli Jönsson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 98/02426

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 29-31
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Claims 29-31 are directed to methods of treatment of the human or animal body by surgery or by therapy/diagnostic methods practised on the human or animal body/Rule 39.1(iv). Nevertheless, a search has been executed for these claims. The search has been based on the alleged effects of the compounds/compositions.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

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